

3. (Amended) The method of claim 1, wherein the stable genetic modification is in a keratinization disorder gene selected from the group consisting of KRT1, KRT10, KRT9, KRT16, LOR, KRT2e, KRT6a, KRT 16, KRT 17, STS, TGM1, GJB2, GJB3, ATP2A2, DSP and DSG1.

4. (Amended) The method of claim 1, wherein the selected gene is tyrosinase, COL7A1, LAMA3, LAMB3, LAMC2, COL17A1, ITGA6, ITGB4, PLEC1, KRT5, KRT14, PKP1, KRT1, KRT10, KRT9, KRT16, LOR, KRT2e, KRT6a, KRT 16, KRT 17, STS, TGM1, GJB2, GJB3, ATP2A2, DSP, DSG1, HR, hHB1, hHB6, PAX3, TYR, TYRP-1, OCA2, OA1, MITF, HPS, FECH, UROS, URO-D, XPA, XPB, XPC, XPD, XPG, PTC, STK11/LKB1, PTEN, PTEN, XPB, XPD, WHN, GLA, ATM, ENG, ALK-1, PPO, BPAG2, or DSG3 gene.

8. (Twice Amended) The method of claim 1, wherein the chimeric RNA-DNA oligonucleotide comprises:

(a) a first string of nucleotides wherein the first string is made of at least four contiguous deoxyribonucleotides flanked on each side by at least nine ribonucleotides; and

(b) a second string of deoxyribonucleotides that is fully complementary to the first string of nucleotides, and

wherein the chimeric RNA-DNA oligonucleotide is, RNase protected, and wherein the chimeric RNA-DNA oligonucleotide has in each of the first and second strings a set of contiguous nucleotides that are fully complementary to a segment of DNA of the selected gene except that the first string has one mismatching deoxyribonucleotide in said contiguous deoxyribonucleotides that defines a site of modification in the selected gene.

9. (Twice Amended) The method of claim 1, wherein the chimeric RNA-DNA oligonucleotide comprises:

(a) a first string of nucleotides wherein the first string is made of at least 20 ribonucleotides; and

(b) a second string of deoxyribonucleotides having the same number of deoxyribonucleotides as in the first string of nucleotides, wherein the second string is fully complementary to the first string of nucleotides except that the second string has a deoxyribonucleotide that forms a mismatched base pair with the corresponding nucleotide in the first string, and

wherein the chimeric RNA-DNA oligonucleotide is RNase protected, and wherein the chimeric RNA-DNA oligonucleotide has in each of the first and second strings a set of contiguous nucleotides that are fully complementary to a segment of DNA of the selected gene except that the deoxyribonucleotide in the second string also forms a mismatched base pair with the corresponding deoxyribonucleotide in the DNA strand of the selected gene which mismatched base pair defines a site of modification in the selected gene.

10. (Twice Amended) The method of claim 1, wherein the chimeric RNA-DNA oligonucleotide comprises:

(a) a first string of nucleotides wherein the first string is made of at least four contiguous deoxyribonucleotides flanked on each side by at least nine ribonucleotides; and
(b) a second string of deoxyribonucleotides that is fully complementary to the first string of nucleotides, and

wherein the chimeric RNA-DNA oligonucleotide is RNase protected, and wherein the chimeric RNA-DNA oligonucleotide has in each of the first and second strings a set of contiguous nucleotides that are fully complementary to a segment of DNA of the selected gene except that the first and second strings have one, two or four pairs of nucleotide insertions or deletions that defines a site of modification in the selected gene.

19. (Amended) The method of claim 18, wherein the selected gene is tyrosinase, COL7A1, LAMA3, LAMB3, LAMC2, COL17A1, ITGA6, ITGB4, PLEC1, KRT5, KRT14, PKP1, KRT1, KRT10, KRT9, KRT16, LOR, KRT2, KRT6, KRT 16, KRT 17, STS, TGM1, GJB2, GJB3, ATP2A2, DSP, DSG1, HR, hHB1, hHB6, PAX3, TYR, TYRP-1, OCA2, OA1,

C-3

MITF, HPS, FECH, UROS, URO-D, PPO, XPA, XPB, XPC, XPD, XPG, PTC, STK11/LKB1, PTEN, PTEN, XPB, XPD, WHN, GLA, ATM, ENG, ALK-1, a cytokine BPAG2 or DSG3 gene.

23. (Twice Amended) The method of claim 18, wherein the chimeric RNA-DNA oligonucleotide comprises:

- (a) a first string of nucleotides wherein the first string is made of at least four contiguous deoxyribonucleotides flanked on each side by at least nine ribonucleotides; and
- (b) a second string of deoxyribonucleotides that is fully complementary to the first string of nucleotides, and

wherein the chimeric RNA-DNA oligonucleotide is RNase protected, and wherein the chimeric RNA-DNA oligonucleotide has in each of the first and second strings a set of contiguous nucleotides that are fully complementary to a segment of DNA of the selected gene except that the first string has one mismatching deoxyribonucleotide in said contiguous deoxyribonucleotides that defines a site of modification in the selected gene.

24. (Twice Amended) The method of claim 18, wherein the chimeric RNA-DNA oligonucleotide comprises:

- (a) a first string of nucleotides wherein the first string is made of at least 20 ribonucleotides; and
- (b) a second string of deoxyribonucleotides having the same number of deoxyribonucleotides as in the first string of nucleotides, wherein the second string is fully complementary to the first string of nucleotides except that the second string has a deoxyribonucleotide that forms a mismatched base pair with the corresponding nucleotide in the first string to make the genetic modifications in the selected gene, and

wherein the chimeric RNA-DNA oligonucleotide is RNase protected, and wherein the chimeric RNA-DNA oligonucleotide has in each of the first and second strings a set of contiguous nucleotides that are fully complementary to a segment of DNA of the selected gene except that the deoxyribonucleotide in the second string also forms a mismatched base pair with

the corresponding deoxyribonucleotide in the DNA strand of the selected gene which mismatched base pair defines a site of modification in the selected gene.

25. (Twice Amended) The method of claim 18, wherein the chimeric RNA-DNA oligonucleotide comprises:

(a) a first string of nucleotides wherein the first string is made of at least four contiguous deoxyribonucleotides flanked on each side by at least nine ribonucleotides; and
(b) a second string of deoxynribonucleotides that is fully complementary to the first string of nucleotides, and

wherein the chimeric RNA-DNA oligonucleotide is RNase protected, and wherein the chimeric RNA-DNA oligonucleotide has in each of the first and second strings a set of contiguous nucleotides that are fully complementary to a segment of DNA of the selected gene except that the first and second strings have one, two or four pairs of nucleotide insertions or deletions that defines a site of modification in the selected gene.

33. (Amended) The animal model of claim 32, wherein the selected skin gene is Tyr, COL7A1, LAMA3, LAMB3, LAMC2, COL17A1, ITGA6, ITGB4, PLEC1, KRT5, KRT14, PKP1, KRT1, KRT10, KRT9, KRT16, LOR, 1998, KRT2e, KRT6a, KRT 16, KRT 17, STS, TGM1, GJB2, GJB3, ATP2A2, DSP, DSG1, HR, hHB1, hHB6, PAX3, TYR, TYRP-1, OCA2, OA1, MITF, HPS, FECH, UROS, URO-D, PPO, XPA, XPB, XPC, XPD, XPG, PTC, STK11/LKB1, PTEN, PTEN, XPB, XPD, WHN, GLA, ATM, ENG, ALK-1, a cytokine BPAG2 or DSG3 gene.